Remarks

Claims 1-52 are pending. Claims 6-52 are withdrawn as being drawn to non-elected inventions.

Drawings

It is respectfully requested that the Examiner acknowledge the drawings as originally filed.

Rejection Under 35 U.S.C. § 102(e)

Claims 1-5 were rejected under 35 U.S.C. § 102(e) as being anticipated by Thompson/U.S. Patent No. 7,029,859 B2. Applicants respectfully traverse this rejection.

As stated in 35 U.S.C. 102(e):

> A person shall be entitled to a patent unless-
>
> > The invention was described in 1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or 2) a patent granted on a n application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

And as stated in the MPEP §2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art."

Thompson generally teaches treatments for various cancers through suppressing expression of the caveolin gene (See for example, col 4, lines 4-13). Further, Thompson teaches treatment of *metastatic* cancers, such as prostate cancer, not primary cancers arising from tissues such as the prostate (See for example, Col 4, lines 36-52). In addition, Thompson teaches

methods utilizing a caveolin antibody to assess the potential of metastatic activity (See for example, Col 4, lines 44-52). Thompson sums up its core teaching stating,

"As embodied and broadly described herein, the present invention is directed to methods for the detection, diagnosis and treatment of disorders related to metastasis . . . [and] caveolin expression correlates with metastasis." (Col 5, lines 15-17 and Col 16, line 24).

Thompson mentions "breast" but only does so in the context of caveolin. For example, Thompson states, "One of the first of such genes identified was the gene for caveolin, a major structural component of an organelle termed caveolae. It has subsequently been confirmed in animal models and in human prostate and breast cancer that increased levels of the caveolin protein are associated with metastasis (Yang, G. et al., Clin. Can. R. 4:1873 1880, 1998)." (Col 18, lines 25-31). Furthermore, Thompson discusses the making of a transgenic mouse overexpressing caveolin and looking at this phenotype in breast tissue (See Example 3).

The only place where Thompson mentions "androgen receptor" is in Example 2, and Thompson provides a correlation between caveolin and androgen/androgen receptor in castration-induced regression of mouse prostate cancer Col 23, lines 4-17). This is done in a castration mouse model, having nothing to do with breast cancer or breast tissue.

Example 2 of the Thompson patent provides how castration-induced regression of mouse prostate cancer leads to an increase in caveolin and androgen receptor levels in tumors grown in these mice. Thompson discusses obtaining prostate cancer cell lines (Col 23, lines 4-25) and assaying for androgen receptor, *but* this relates to prostate cancer, not breast cancer. Nothing in Thompson teaches a correlation between androgen receptor and breast cancer. Example 2, relied on by the Examiner, does not even mention breast cancer. Thompson did not use the identification of androgen receptor to screen for the presence of prostate cancer but instead identified androgen receptor in known prostate cancer subjects. The present claims use the identification of androgen receptor to screen for the increased risk or presence of breast cancer.

The current claims specifically state "...wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer." Since Thompson does not teach a correlation between androgen receptor and breast cancer, it fails to anticipate the present claims and thus fails to satisfy 35 U.S.C. 102(e). Applicant respectfully requests withdrawal of this rejection as it pertains to all of the rejected claims.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 2, 4 and 5 were rejected under 35 U.S.C. § 102(b) as being anticipated by Fujimoto et al. (Laboratory Investigation 80(9):1465-1471, 2000). Applicants respectfully traverse this rejection.

As stated in 35 U.S.C. 102(b):

> A person shall be entitled to a patent unless-
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> > The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

And as stated in the MPEP §2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art."

Fujimoto et al. describe the expression of androgen receptor in advanced Extramammary Paget's Disease (EMPD). Fujimoto et al. do not teach the presence of androgen receptor being indicative of an increased risk or presence of breast cancer, as their disclosure is on EMPD not breast cancer. EMPD is not breast cancer and does not teach or suggest breast cancer. Therefore, every element of the current claims are not found in the alleged prior art.

Fujimoto et al. assay tissue samples for androgen receptor and indicate that androgen receptor is one of the hormone receptors responsible for the development and growth of EMPD.

A tissue sample is obtained and androgen receptor is assayed for but Fujimoto et al. clearly describes this with regards to EMPD, not breast cancer.

The current claims specifically state "...wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer." Since Fujimoto does not teach a correlation between androgen receptor and breast cancer, it fails to 35 U.S.C. 102(b) and therefore these claims are not anticipated.

Applicant respectfully requests withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102(a)

Claims 1, 2, and 4 were rejected under 35 U.S.C. § 102(a) as being anticipated by Moinfar et al. (Cancer 98(4):703-711, 2003). Applicants respectfully traverse this rejection.

As stated in 35 U.S.C. 102(a):

> A person shall be entitled to a patent unless-
>
> The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.

And as stated in the MPEP §2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art."

Moinfar et al. investigated the expression of androgen receptor in breast carcinomas and described the correlations with other hormone receptors and Her-2 expression. Moinfar et al. do *not* describe a correlation between androgen receptor and the increased risk or presence of breast cancer. Therefore, every element of the current claims are not found in the alleged prior art.

Moinfar begins by saying,

> Although numerous studies have examined ER and PR and their correlations with other prognostic indicators, surprisingly

> little is known about the role of androgen receptor (AR) and its prognostic value in breast carcinoma. Page 704, 1st column

Moinfar goes on to state,

> The aim of the current study was to investigate the expression of AR in a large series of breast carcinomas using immunohistochemical techniques. The results were analyzed for correlations with ER, PR, and HER-2/neu expression, as determined immunohistochemically in tissue sections from paraffin-embedded archival material. Page 704, 1st column

Note the statement of what is known about AR and breast cancer ("surprisingly little") and that the "aim" was not to identify AR as a prognosticator, but to "analyze correlations with ER, PR, and Her2/neu."

Moinfar found that

> AR was expressed in nearly all G1 tumors (95%) but was expressed somewhat less frequently in G2 and G3 DCIS. Moinfar at page 705 2nd col.

Thus, as the tumor is getting worse (i.e. the grade of the tumor is increasing) AR is decreasing[1]. The first column on page 706 of Moinfar supports this conclusion stating,

> Her-2/neu showed an increase in overexpression frequency with increasing tumor grade, from 0% in G1 ICAs, to 26% in G2 ICAs and 42% in G3 ICAs. Page 706, 1st col.

Her-2/neu is today one of the most predictive indicators of breast cancer carcinomas[2], and as proclaimed in Moinfar, AR in breast carcinomas is *decreasing* as the tumor progresses and

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[1] Applicants have attached the definition of Tumor Grading obtained from wikipedia on February 3, 2010, (Appendix A) which shows that G1, G2, and G3 refer to a tumor grade, and that as the number goes up the cancer is getting worse. See for example, definitions of GX Grade cannot be assessed, G1 Well differentiated (Low grade), G2 Moderately differentiated (Intermediate grade), G3 Poorly differentiated (High grade), G4 Undifferentiated (High grade).

[2] See for example, Appendix B, a print out of the wikipedia definition for Her2/neu printed on February 20, 2010, which states, "Because of its prognostic role as well as its ability to predict response to trastuzumab (Herceptin US brand name) (see below), breast tumors are routinely checked for overexpression of HER2/neu."

gets worse. Again, note the present claims focus on the "presence" of AR, not the absence or loss.

This is a clear teaching away from AR as a prognosticator for breast cancer, and thus teaches away from the present claims requiring "wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer" and "identifying the subject as having an increased risk of breast cancer when the presence of androgen receptor is identified." Teaching away provides one of the best indicators of non-obviousness[3], as well as logically indicating that Moinfar did not anticipate the present claims. In fact, Moinfar failed to show the hoped for conclusion cited above, stating,

> Statistical analysis of the results of the current study showed that in both DCIS and invasive carcinomas, AR was expressed independently of tumor grade as well as ER, PR, and HER-2/neu status. Page 710, 1st col.

As ER, PR, and HER-2/neu are well known and accepted breast tumor markers, and tumor grade is an important diagnostic, the fact that AR is expressed independently of all of these would indicate that it is *not* a diagnostic for breast cancer, as the skilled artisan would expect tumor markers that indicate the presence of a tumor to express together.

While Moinfar et al. may detect the presence of androgen receptor in samples of breast carcinomas, Moinfar et al. does not disclose a method of screening a subject <u>for</u> breast cancer. There is a clear difference between screening a subject *for* breast cancer and screening a subject *with* breast cancer. In Moinfar et al., the test samples are known breast carcinomas, therefore the presence of androgen receptor cannot be used to indicate the risk of breast cancer (as cancer has already been diagnosed) or the presence of breast cancer (as it is already known cancer is present). The subject in Moinfar et al. is different than the subject in the present application since androgen receptor is identified in a subject that has already been diagnosed with breast

[3] "Teaching away" is a further indicia of non-obviousness which is properly considered in regards to an obviousness rejection, *In re Hedges*, 228 USPQ at 687.

cancer in Moinfar et al. and androgen receptor is identified in a subject that is being screened for the possibility of breast cancer in the current claims.

Furthermore, the identification of androgen receptor in Moinfar et al. is not used as an indicator of increased risk or presence of breast cancer. The identification of androgen receptor was compared to other tumor variables. Moinfar et al. did not disclose the use of unknown samples and determine the risk or presence of breast cancer based on identification of androgen receptor. The current claims specifically state "...wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer." Thus, Moinfar et al. does not teach every element of the claimed invention and therefore does not anticipate the current claims and does not satisfy 35 U.S.C. § 102(a).

Applicant respectfully requests withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103

Claims 1-5 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Fujimoto et al., in view of Thompson/U.S. Patent No. 7,029,859. Applicants respectfully traverse this rejection.

A. Obviousness standard

The Supreme Court, in *KSR v. Teleflex*, (*KSR International Co. v. Teleflex Inc. et al.*, 127 S. Ct. 1727 (2007), reaffirmed that obviousness should be determined using the framework set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR, at 1734.

Specifically, an Office Action must state a *prima facie* case of obviousness, and a failure to provide the appropriate motivation linked to the reasonable expectation of success is required to meet this for *chemica/biotechnology* related inventions post *KSR*.

In support of this the Examiner is directed to *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Federal Circuit in *Takeda* found claims to compounds non-obvious over the close "lead compound" prior art, which differed by mere atoms, because the skilled artisan would not be led to modify the closest compound for the property, *the unclaimed property,* providing a specific utility for the compounds. The compounds were found to have the specific property of antidiabetic activity, which was not recited in *Takeda's* claim 1, a rejected claim. The art did not recognize this activity, and the court found that it would not be obvious because there was not a suggestion to start with the lead compound for the desired purpose, which is why a skilled artisan would modify the compound.

With respect to an expectation of success, the Office Action misapplies the standard of a reasonable expectation of success. As elaborated on in *Takeda* and further set forth in *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 360 (Fed. Cir. 2007), *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.,* 533 F.3d 1353, 1357 (Fed. Cir. 2008), *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985), and *Proctor & Gamble Comp. v. Teva Pharmaceuticals USA Inc.*, Slip opinion 2008-1404, 1406, and 1408 (Fed. Cir. 2009)[4] in chemical cases, the reasonable

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[4] The Federal Circuit has held that a reasonable expectation of success should be present for a "composition" to be obvious under *KSR* and that the unpredictability of pharmaceutical compositions makes this a difficult hurdle to clear.

The Federal Circuit has found stated

> [To find a composition obvious a court must find that] . . .a person having ordinary skill in the art would have had "reason to attempt to make the composition" known as risedronate and "a reasonable expectation of success in doing so.

expectation of success is filtered through the predictability of the invention, which is defined by the claims. Thus, it is not obvious to arrive at the claimed methods, having the limitation, "identifying the subject as having an increased risk of breast cancer when the presence of androgen receptor is identified," just as in *Takeda* the claimed compound was not obvious for an *inferred* utility. Therefore, the Office Action fails to set forth a *prima facie* case of obviousness as required, and the Applicants traverse this rejection.

Notwithstanding the lack of a *prima facie* case of obviousness, Applicants provide the arguments and facts discussed below in rebuttal, assuming a *prima facie* case has been made.

B. Analysis

The Office Action fails to make a prima facie case of obviousness, for failure to state a motivation or suggestion to combine Fujimoto et al. and Thompson. Furthermore, there has been no evidence provided that one would have a reasonable expectation of success in using androgen receptor as a breast cancer prognosticator.

The references focus on EMPD (not breast cancer) and prostate cancer respectively. There is no suggestion or motivation to move from the conclusion of androgen receptor's presence in EMPD and prostate cancer cells to the conclusion of androgen receptors presence in breast cancer cells, much less that its presence provides an indication about the presence of breast cancer itself. As previously stated, Fujimoto et al. describe the expression of androgen receptor in advanced EMPD. Thompson describes the correlation between caveolin and androgen/androgen receptor in castration-induced regression of mouse prostate cancer. Thompson did not even use the identification of androgen receptor to screen for the presence of

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PharmaStem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342, 1360 (Fed. Cir. 2007)." Furthermore, the Federal Circuit has indicated that to determine whether a composition which was a derivative was obvious a showing that the specific modifications would have been suggested is needed. (See *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008), *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), and *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)). The Federal Circuit has also focused on unpredictability as an indicator of a lack of expectation of success. (See *Proctor & Gamble Comp. v. Teva Pharmaceuticals USA Inc.*, Slip opinion 2008-1404, 1406, and 1408 (Fed. Cir. 2009).

prostate cancer (much less for breast cancer) but instead identified androgen receptor in known prostate cancer subjects. Neither Fujimoto et al. nor Thompson teach or suggest the presence of androgen receptor being indicative of an increased risk or presence of breast cancer. There is no suggestion or motivation in Fujimoto or Thompson to combine their teachings to arrive at the claimed technology as it is drawn to breast cancer.

Furthermore, to Applicant's knowledge, there has not been a relationship identified between castrated males and breast cancer and thus combining art related to castrated males and prostate cancer with any other art, particularly Fujimoto et al., would not have a reasonable expectation of success. The fact that Thompson's studies were performed in castrated male mice would not lead one of skill in the art to identify androgen receptor in a subject and correlate its presence with breast cancer. The skilled artisan would not have thought to combine Thompson and Fujimoto et al. in order to achieve the claimed results.

Thus, the Office Action fails to make a *prima facie* case of obviousness over Fujimoto et al. and Thompson.

Notwithstanding the above, assuming arguendo that Fujimoto et al. and Thompson make a *prima facie* case of obviousness, secondary considerations rebut a finding of obviousness.

The focus of Fujimoto et al. on EMPD specifically teaches away from breast cancer as EMPD is found mostly in the perineum, vulva, axilla, scrotum, and penis. The name itself, *Extramammary* Paget's Disease, implies something outside of the mammary or breast. There is no teaching, suggestion or motivation to pursue the current claimed invention, correlating the presence of androgen receptor and an increased risk of or presence of breast cancer. The mere identification of androgen receptor in tumors related to a disease other than breast cancer does not make it obvious to assay for the presence of androgen receptor and correlate it with an increased risk of or presence of breast cancer due to the vast differences among different diseases and more importantly among different types of cancer.

Likewise, Thompson focuses on the caveolin-1 gene. Thompson does not focus on the presence of androgen receptor. There is no indication that androgen receptor has any prognostication value even for prostate cancer, much less for breast cancer. Thompson taken as a whole would push a researcher at best to look for the caveolin gene in breast cancer, assuming there was a valid reason to link breast cancer to prostate cancer. The skilled artisan understands how different not only one cancer can be between individuals but particularly how different two cancers from different tissues can be. Therefore, one would not assume that the increased presence of androgen receptor in tumor cells in a castrated mouse would be equivalent or similar to identifying and correlating androgen receptor with breast cancer, even if androgen receptor was the focus of Thompson.

Thus, Applicant respectfully traverses this obviousness rejection and request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103

Claims 1-5 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Moinfar et al., in view of Thompson/U.S. Patent No. 7,029,859. Applicants respectfully traverse this rejection.

As previously stated, Moinfar et al. identify androgen receptor in known breast carcinomas and correlate this to the presence of estrogen and progesterone receptors and Her-2/neu expression. Applicant notes that Moinfar et al., as well as Thompson, does not disclose the current claim set since, *inter alia*, they screen subjects *with* breast carcinoma by identifying androgen receptor while the current claims screen subjects *for* breast cancer by identifying androgen receptor. Importantly, even though Moinfar et al. looked for androgen receptor in breast cancer cells, Moinfar et al. itself makes no suggestion or provides no motivation to use androgen receptor's *presence*, to predict breast cancer.

Moinfar also fails to provide a reasonable expectation of success for use of androgen receptor as a breast cancer prognosticator. As discussed above, Moinfar et al. teaches expression

relationships between Her2/neu and other molecules. However, these relationships, as taught by Moinfar et al. are not linked with breast cancer, and the relationships are not predictable with respect to the molecules themselves and androgen receptor and cancer, i.e. there is no foreseeable correlation with breast cancer. This cannot provide a reasonable expectation of success to the skilled artisan for claims drawn to using the presence of androgen receptor to identify subjects at risk for breast cancer.

The combination of Moinfar et al. with Thompson fails to provide a *prima facie* case of obviousness as there is no suggestion or motivation provided by Moinfar et al. or Thompson (discussed above) and there is no reasonable expectation of success provided by the teachings of Moinfar et al. or Thompson (discussed above) for a method of identifying subjects at risk for breast cancer.

Notwithstanding the above, assuming arguendo that Moinfar et al. and Thompson make a *prima facie* case of obviousness, secondary considerations rebut a finding of obviousness.

As discussed above Thompson teaches away from a method "wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer." Likewise Moinfar teaches away. Moinfar compares androgen receptor expression to molecules that have known relationships to breast cancer and does not find a correlation or relationship that would lead to androgen receptor being a breast cancer prognosticator. For example, as the stage of breast cancer gets worse, androgen receptor as taught by Moinfar either decreases or is unpredictable in its expression. The present claims are focused on the presence of androgen receptor, not the loss of androgen receptor, or certainly the unpredictable expression of androgen receptor.

The alleged prior art does not teach or suggest what is currently claimed. The present claims state that one will assay for the presence of androgen receptor, "wherein the presence of androgen receptor indicates an increased risk of or presence of breast cancer." This can not be found in Moinfar et al. or Thompson nor would the combination of this art lead to this result.

Both Moinfar et al. and Thompson assay for the presence of androgen receptor but neither of them use androgen receptor as an indicator for the increased risk or presence of breast cancer.

Thus, Applicant respectfully traverses this obviousness rejection and request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A deposit order account charge made electronically in the amount of $555.00, representing $555.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(2) and a Request for Extension of Time under 37 CFR 1.136 for a three month extension of time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

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